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Cardiovascular Neural Regulation Explored in the Frequency Domain

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This article discusses the clinical application and potentiality of a relatively new methodology, which in large part uses noninvasive recordings and appears to provide a quantitative evaluation of the sympathovagal interaction modulating cardiovascular function.

As a result of this methodology, pathophysiological conditions of paramount importance, such as arterial hypertension, myocardial ischemia, sudden cardiac death, and heart failure, for which the promoting or aggravating role of neural factors is still largely unknown, might soon undergo a novel scrutiny with practical implications.

Physiological Background

In addition to cardiac cycle, two main rhythmic events affect the circulation: respiration and vasomotion. The respiratory activity has long been known to be accompanied by arterial pressure¹ and heart period fluctuations, whereas the finding of slow arterial pressure oscillations (also referred to as Mayer waves), having a period of approximately 10 seconds, has been more elusive.²⁻⁴ On the other hand, rhythmic discharges in phase with respiration have been described in the sympathetic⁵ and vagal^{6,7} outflows; similarly, a slower rhythm in phase with vasomotor waves has been found in the sympathetic^{8,9} and vagal¹⁰ efferent discharges.

The neural regulation of circulatory function is mainly effected through the interplay of the sympathetic and vagal outflows. In most physiological conditions, the activation of either outflow is accompanied by the inhibition of the other. The sympathovagal balance is tonically and phasically modulated by the interaction of at least three major factors: central neural integration, peripheral inhibitory reflex mechanisms (with negative feedback characteristics), and peripheral excitatory reflex mechanisms (with positive feedback characteristics)¹¹⁻¹³ (Figure 1).

It is the core hypothesis of the proposed approach that this balance, viewed as a reciprocal relation, can on the whole be explored in the frequency domain. That is, variable phenomena such as heart rate and arterial blood pressure can be described not only as a function of time (i.e., in the time domain), but they can also be described as the sum of elementary oscillatory components, defined by their frequency and amplitude. We review data that support the assumptions that 1) the respiratory rhythm of heart period variability, defined as the high-frequency (HF) spectral component, is a marker of vagal modulation; 2) the rhythm corresponding to vasomotor waves and present in heart period and arterial pressure variabilities, defined as the low-frequency (LF) component, is a marker of sympathetic modulation; and 3) a reciprocal relation exists between these two rhythms that is similar to that characterizing the sympathovagal balance.

Methodology

Figure 2 schematically illustrates the procedure of spectral analysis of heart period variability as performed in our laboratory. A similar procedure is used for other signals, such as arterial pressure (Figures 3 and 4), respiration, or nerve discharge (Figure 5). From the original electrocardiographic signal, a digital computer stores the time intervals between consecutive peaks of the R waves as the tachogram. In principle, the subsequent spectral analysis, used to detect possible rhythmicity hidden in the signal, necessitates stationary conditions that, in strict terms, are unknown to biology. Thus, a practical compromise has to be found between the length of event series and theoretical mathematical requirements.¹⁴ Under adequate stationary conditions, the tachogram is not accompanied by slow trends or step changes (see Figure 2).

Various algorithms¹⁵ can be used at this stage to assess the number, frequency, and amplitude of the oscillatory components. Most studies have relied on either the fast Fourier transform algorithm¹⁶⁻¹⁹ or an autoregressive approach.²⁰⁻²² The former is easy to implement but requires strict periodicity of the data and is frequently used with an a priori selection of the number and frequency range of oscillatory components. Autoregressive algorithms (e.g., Figure 2)

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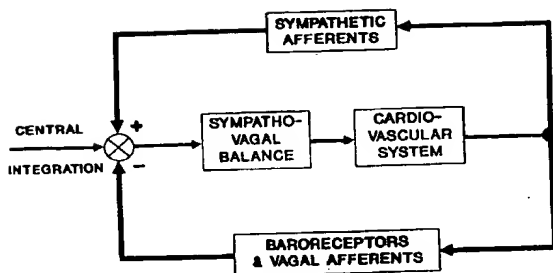


FIGURE 1. Schematic representation of opposing feedback mechanisms that, in addition to central integration, subserve neural control of the cardiovascular system. Baroreceptive and vagal afferent fibers from the cardiopulmonary region mediate negative feedback mechanisms (exciting the vagal outflow and inhibiting the sympathetic outflow), whereas positive feedback mechanisms are mediated by sympathetic afferent fibers (exciting the sympathetic outflow and inhibiting the vagal outflow).

can automatically furnish the number, amplitude, and center frequency of the oscillatory components without requiring a priori decisions. Because short segments of data are more likely to be stationary, the autoregressive algorithms, which are capable of operating efficiently even on shorter series of events, appear to provide an additional advantage.

The spectrum of Figure 2 contains three components, with frequencies centered at 0.00 Hz (component 1), 0.12 Hz (component 2), and 0.27 Hz (component 3), respectively. The study of the very low frequency (0–0.03 Hz) phenomena (component 1), which might contain clinically relevant information, requires specific methodologies and long periods of uninterrupted data.^{23,24} Thus, component 1, considered DC, is not addressed in the present methodology. Components 2 and 3, labeled LF and HF, respectively, are evaluated in terms of frequency

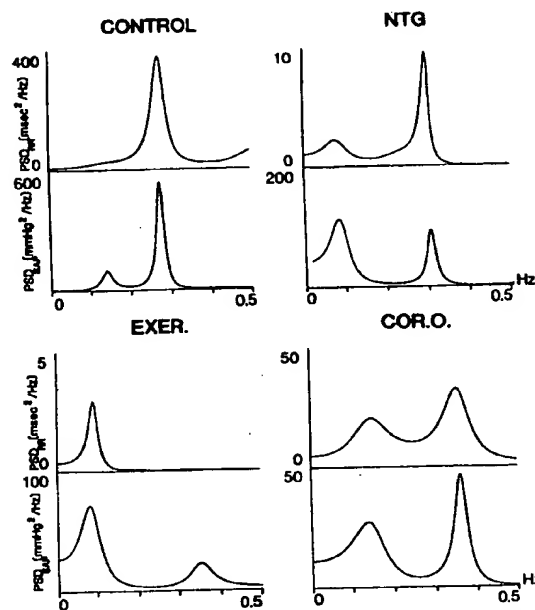


FIGURE 3. Spectral analysis of RR interval (upper tracings in each panel) and systolic arterial pressure (SAP) (lower tracings in each panel) variabilities in conscious dogs at rest (CONTROL) and during experimental maneuvers leading to a sympathetic predominance (i.e., nitroglycerin infusion [NTG], treadmill exercise [EXER.], and transient acute coronary artery occlusion [COR.O.]). Note at control the presence of a single major high-frequency component in the RR interval autospectrum; in SAP, a smaller low-frequency component is also evident. During sympathetic activation, spectral distribution is altered in favor of low frequency; simultaneously, a drastic reduction in RR variance occurs (notice different scales on ordinates). PSD, power spectral density. From References 30 and 107 and unpublished material.

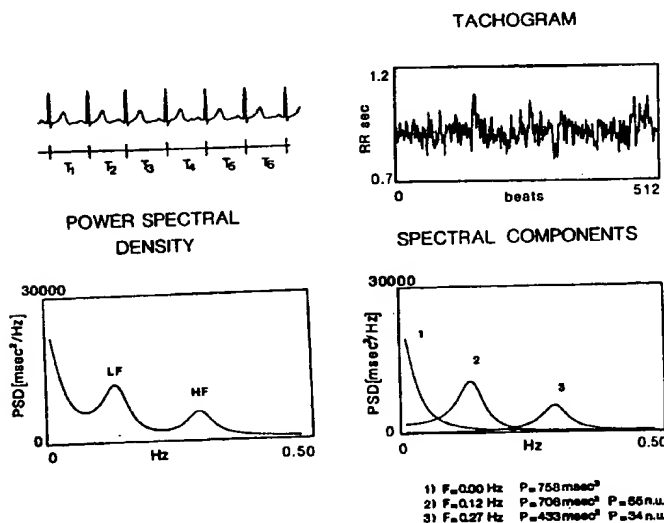


FIGURE 2. Schematic representation of the method used for the spectral analysis of RR interval variability. From the surface electrocardiogram (top left panel), the program computes the individual RR intervals (T_1-T_0) and stores them in the memory as the tachogram. From the tachogram, power spectral density (PSD) is computed. Two major components, low frequency (component 2) and high frequency (component 3), are usually recognized as well as a large and variable fraction of very slow oscillations (below 0.03 Hz, component 1), which is not considered in the analysis. Note that the computer program automatically recognizes and prints out for each component the center frequency (F) and associated power (P) in absolute (msec²) and normalized units (n.u.) (see values in lower right panel). In the ordinates of lower panels, PSD units are in msec²/Hz; consequently, their integrated value corresponding to the area (i.e., power, obtained over any given frequency range in Hz) is expressed in msec². Reproduced with permission from Reference 26.

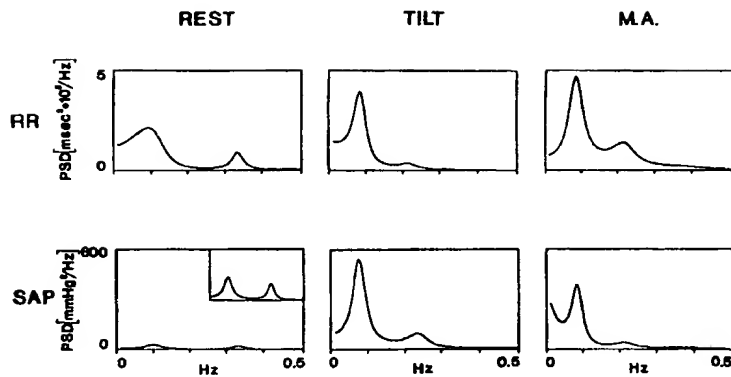


FIGURE 4. Spectral analysis of both RR interval and systolic arterial pressure (SAP) variabilities in a human subject at rest, during passive tilt, and during a mental arithmetic test (M.A.). Note the presence at rest of two major spectral components in both RR and SAP variabilities (in SAP variability, a $\times 10$ magnified spectrum is provided in inset). During tilt and M.A., there is a marked predominance of low-frequency component in both RR and SAP autospectra. PSD, power spectral density. From Reference 26 and unpublished material.

(hertz in the figures) and amplitude. This amplitude is assessed by the area (i.e., power) of each component; therefore, squared units are used for the absolute value (milliseconds squared in Figure 2). In addition, normalized units (NU) are obtained by dividing the power of a given component by the total variance (from which component 1 has been subtracted) and multiplying by 100 (Figure 2). LF and HF components can also be found in the spectra of systolic arterial pressure (SAP) variability^{22,25,26} (Figures 3 and 4) and of sympathetic and vagal efferent nerve discharges²⁷ (Figure 5). A recursive version of this methodology permits the analysis of recordings over a 24-hour period.^{25,26,28,29}

Like the HF respiratory component, LF oscillation does not have a fixed period, and its center frequency can vary considerably (from 0.04 to 0.13 Hz).^{26,30} Therefore, the convention of subdividing the low part of the spectrum into two preselected bands¹⁶⁻¹⁸ with a cutoff frequency of 0.07–0.09 Hz^{28,29,31} contained within the range of LF component appears unjustified.

Finally, it should be mentioned that from the simultaneous spectral analysis of RR interval and SAP

variabilities,^{19,32} a quantitative assessment of the overall gain of the baroreceptor mechanisms can be obtained.³³⁻³⁵ In our studies,^{25,33} this gain is represented by the index (α), which can be computed in correspondence to either LF or HF components. Its numerical value is provided by the square root of the ratio of the powers of RR to corresponding SAP spectral components.²⁵ In dynamic conditions, arterial pressure should be recorded with high-fidelity techniques,^{25,26,36} whereas, in resting conditions, measurements with standard catheter-manometer systems^{25,35} or noninvasive plethysmographic devices¹⁹ can be adequate.

Comparable results were obtained²⁵ when the gain of the baroreceptor mechanisms was evaluated with both the index (α) and the phenylephrine method,³⁷ which is based on the slope of the reflex bradycardia accompanying a transient arterial pressure rise induced by intravenous injection of a pressor drug.

Animal Studies

A dominant role of the vagi in determining the HF component of RR variability was inferred from experiments in acute decerebrate cats³⁸ and conscious

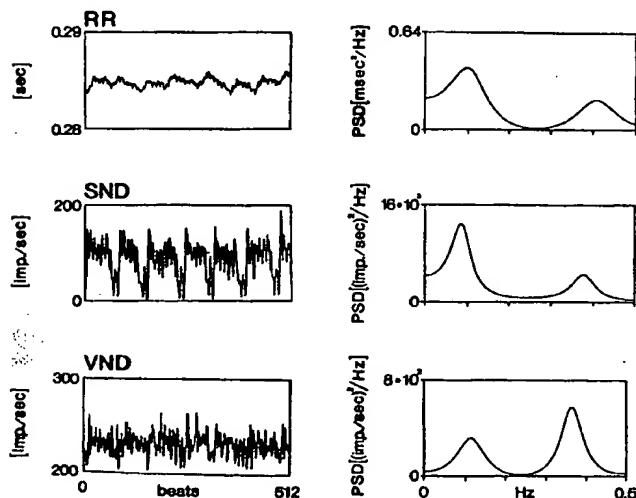


FIGURE 5. Spectral analysis of RR interval, preganglionic sympathetic neural discharge (SND) recorded from third left thoracic sympathetic ramus communicans, and efferent vagal neural discharge (VND) simultaneously recorded from left cervical vagus in an artificially ventilated decerebrate cat. Time series of the three signals are illustrated on left panels, whereas their autospectra are represented on right panels. A predominant low frequency characterizes RR and SND autospectra, whereas a greater respiratory high-frequency component is present in VND variability. PSD, power spectral density. From Reference 27 and unpublished material.

dogs^{18,30,39,40} describing the effects of vagotomy and muscarinic receptor blockade.

Recently, Rimoldi et al³⁰ reported that in resting conscious dogs characterized by a marked HF predominance (Figure 3) resulting from high vagal tone,^{41,42} a small LF component was always present in SAP variability but was present in only 50% of the cases in RR variability. However, an important finding was that whenever sympathetic excitation occurred, such as during baroreceptor unloading with nitroglycerin infusion, transient coronary artery occlusion, or physical exercise (Figure 3), a significant increase in LF was observed. The role played by baroreceptive mechanisms in these various experimental conditions was probably different because arterial pressure was reduced by nitroglycerin infusion, unchanged during myocardial ischemia, and increased with exercise. Therefore, LF component should not be considered a specific reflection of a baroreflex compensatory response⁴³ but rather a general marker of sympathetic excitation, regardless of its mechanism.

During muscarinic receptor blockade,³⁰ which drastically reduced total RR variance, all of the remaining power in control conditions and during baroreceptor unloading was concentrated in the LF region, in accordance with the sympathetic predominance induced by the drug. Finally, after chronic bilateral stellectomy producing cardiac sympathetic denervation, baroreceptor unloading no longer induced an increase in the LF component of RR variability. On the contrary, the increase in the LF component of SAP variability was still present.^{22,30}

It was inferred that in RR variability, HF was mainly mediated by vagal mechanisms, whereas the sympathetic outflow appeared essential to the LF increases. Furthermore, the importance of neural mechanisms in mediating LF and HF of RR variability and LF of SAP variability was proven³⁰ by their disappearance during ganglionic transmission blockade obtained with intravenous infusion of trimethaphan.

To conclude on the most relevant results from animal experiments, which appear to validate the proposed approach, we emphasize that both LF and HF components can be directly and simultaneously detected from the sympathetic and vagal efferent impulse activities. In the example of Figure 5, the spectral analysis of RR, sympathetic, and vagal variabilities reveals corresponding LF and HF components, with a predominance of LF in the sympathetic discharge and of HF in the vagal activity. This fact, on the one hand, stresses that spectral analysis can be used to examine the complexities of neural regulation without artificially isolating the influence of either outflow and, on the other hand, suggests that a rhythm, being a flexible and dynamic property of neural networks,^{44,45} should not necessarily be restricted to one specific neural pathway to carry a functional significance.

Human Physiological Studies

Use of LF and HF Components to Assess Sympathovagal Balance

The total power of RR interval variability (i.e., variance) has been interpreted as a selective index of cardiac parasympathetic tone^{46,47}; however, in conditions characterized by an augmented sympathetic activity, it does not always appear to be capable of reflecting the balance with the concomitant vagal withdrawal.^{22,48-50}

In the resting normal subject, power spectral analysis reveals two main rhythmic oscillations in heart period and arterial pressure variabilities^{22,25} (Figures 2 and 4). LF component usually has a center frequency of approximately 0.1 Hz (0.12 Hz in Figure 2), whereas HF component, synchronous with respiration, occurs at approximately 0.25 Hz (0.27 Hz in Figure 2). The power of the LF component is greater than that of HF in RR variability with an LF-to-HF ratio of usually more than 1.^{22,48,49}

Effects on RR Variability of Maneuvers Enhancing Sympathetic Drive

Passive tilt or, more simply, standing up is accompanied by an increase in the LF and a decrease in the HF component of RR variability (Figure 4).^{20,22,48,49,51-54} The LF-to-HF ratio is greatly enhanced, to values as great as 20 in young subjects.²²

Mental stress induced by arithmetic calculation has been shown to enhance sympathetic activity and alter the sympathovagal balance. This is reflected by a reduction in total power,^{55,56} an increase in LF, and a decrease in HF (Figure 4).^{57,58}

Physical exercise increases sympathetic activity and is associated with various factors such as enhanced respiratory activity, decreased variance, and increased non stationarity, all of which might contribute to a difficult analysis. Although Pagani et al²⁵ described, for mild levels of exercise, a clear predominance of the LF component in RR variability, this phenomenon has been negated by Arai et al.⁵⁹ In general, however, when a sympathetic activation is accompanied by an abatement of RR variance, as takes place physiologically during physical exercise, pharmacologically after atropine administration, or in various pathophysiological conditions, it is crucial to peruse where the residual power is distributed: The state of the balance would still be reflected by the relation between LF and HF components.

Effects on RR Variability of Maneuvers Enhancing Vagal Drive

A nonlinear relation exists between respiration and sinus arrhythmia⁶⁰; however, controlled respiration at frequencies within the resting physiological range⁶⁰ provides a convenient tool to enhance the vagal modulation of heart rate,^{22,51} probably also achieved through the synchronization of all respiratory components. In concrete terms, the power of the HF component becomes predominant at rest during

metronome breathing, leading to an LF-to-HF ratio of less than 1.²² Furthermore, during controlled respiration, increases in the LF component and LF-to-HF ratio observed with tilt are markedly blunted in regard to that obtained during spontaneous respiration.²² If the frequency of controlled breathing is decreased enough to approach LF rhythm, the two components merge into one more powerful oscillation.⁶⁰ In general, all of the studies that have been performed under controlled respiration in the broad range of 0.20–0.30 Hz were likely to be characterized by a sympathovagal balance shifted in favor of the vagal component.^{51,61–63}

Effects on RR Variability of Aging

RR variance has been shown to decrease as age increases^{22,64–67}; however, the LF-to-HF ratio, when measured with autoregressive algorithms, appears unchanged.²² The increase in LF and the reciprocal decrease in HF of RR variability during tilt are also spared by aging, although they are blunted in their magnitude.²² Changes in spectral components induced by standing were more difficult to determine in the elderly with a fast Fourier transform algorithm (see "Methodology"), probably as a consequence of the reduced variance and the low signal-to-noise ratio.^{61,66,67}

Pharmacological Blockades, Neural Lesions, and RR Variability

From the observations by Selman et al⁶⁸ it became clear that atropine administration was capable of practically abolishing the respiratory component of RR variability; this finding was corroborated by the study of Pomeranz et al.⁵¹ On the basis of these studies as well as animal studies, the relation between vagal activity and HF component of RR variability has become generally accepted.

However, there has been disagreement in the literature regarding the interpretation of the LF component. In the same study by Pomeranz et al,⁵¹ intravenous administration of atropine in supine patients under controlled respiration was also capable of reducing the LF component by 84%; it was concluded that in this position, the LF component is mediated entirely by the parasympathetic system. However, because metronome breathing markedly enhances vagal drive and decreases the LF component,²² this general statement is unlikely to be valid in the case of spontaneous respiration.

Furthermore, Inoue et al⁶⁹ noticed that in tetraplegic patients, the LF component was absent and HF was well preserved. They concluded that the absence of the LF component was likely to depend on the interruption of the spinal pathways connecting supraspinal centers with the peripheral sympathetic outflow.

Regarding the effects of β -adrenergic receptor blockade, Pagani et al²² observed that although acute intravenous administration of propranolol blunted only the LF increase induced by tilt, as described by Pomer-

anz et al,⁵¹ chronic oral administration significantly reduced the LF component (evaluated in NU) both at rest and during tilt. The fact that the LF component was clearly reduced but not abolished after chronic β -blockade, which differs with observations in tetraplegic patients,⁶⁹ might be a result of either the incompleteness of a pharmacological blockade in the clinical setting or a different basal contribution of vagal activity.

SAP Variability

The LF component has been reported to increase during tilt,^{22,70} mental stress⁵⁷ (Figure 4), and physical exercise.^{25,70}

During physical exercise, the analysis of SAP variability appears particularly suited to demonstrate an increased sympathetic drive because both its total variance and the LF component remain elevated, at least in correspondence with the mild levels of activity that have been examined so far.^{25,26,30,70} On the other hand, in these conditions, the HF component of SAP variability is likely to depend mostly on mechanical effects of respiration,^{26,30,71} because vagal modulation of RR interval with its resultant effects on stroke volume and arterial pressure should be nearly abolished during exercise.

Continuous 24-Hour Recording of RR and SAP Variabilities

Since initial observations,⁷² a clear circadian oscillation has appeared to characterize the sympathovagal balance.²⁵ In more detail, the LF component of SAP variability increased abruptly with waking up²⁶ while the subjects were still lying in bed; remained elevated during the day,^{26,29} especially in correspondence with physical exercise²⁶; and then underwent a final marked reduction during the night.^{26,29}

A similar circadian pattern in which LF and HF components of RR variability underwent reciprocal changes during the 24 hours could also be assessed with electrocardiographic Holter monitoring²⁶ (Figure 6, left panels). Conversely, in a study in which the LF range was subdivided into two predetermined bands of interest, separated arbitrarily at 0.07 Hz, and the heart period was derived from ambulatory arterial pressure recordings obtained with a system of narrow frequency response, Parati et al²⁹ did not detect in normal subjects the circadian pattern of LF component ("mid frequency" is the term used by the authors).

Human Pathophysiological Studies

Arterial Hypertension

It is an appealing hypothesis that essential hypertension, at least in its early stages, is largely based on increased sympathetic activity.^{13,73} In a study⁵³ comparing hypertensive patients with normotensive age-matched controls, it was found that in RR variability, under resting conditions LF was greater (LF, 68 ± 3 versus 54 ± 3 NU) and HF was less (HF, 24 ± 3 versus 33 ± 2 NU) in hypertensive patients, suggesting an enhanced sympathetic activity and a reduced vagal activity. In hypertensive patients, passive tilt pro-

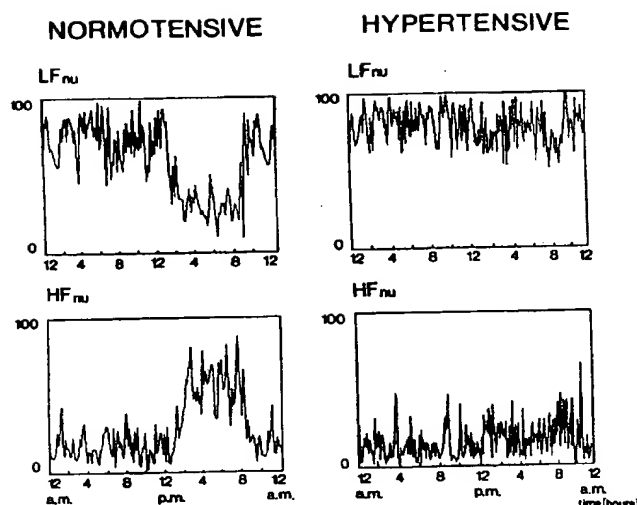


FIGURE 6. Computer analysis plots of 24-hour RR interval variability (Holter recordings) in a normotensive subject (32-year-old man with 110/70 mm Hg resting arterial pressure) and a hypertensive subject (37-year-old woman with 160/105 mm Hg resting arterial pressure). Low-frequency (LF) and high-frequency (HF) components are represented in normalized units (nu). Note that a clear circadian cycle of both spectral components is present in only the normotensive subject. From Reference 74 and unpublished material.

duced smaller increases in LF (Δ LF, 6.3 ± 3 versus 26 ± 3 NU) and decreases in HF (Δ HF, -7.5 ± 2 versus -21.5 ± 2 NU) than in normotensive controls. Furthermore, the values of LF at rest and the altered effects of tilt on LF and HF were significantly correlated with the degree of the hypertensive state, suggesting a continuum distribution.

When RR variability was studied throughout the 24-hour period with the use of Holter recordings, patients with essential hypertension were characterized by the loss of the circadian rhythmicity of the LF component (Figure 6, right panels), whereas a small nocturnal increase in HF was still detectable.⁷⁴ These data, although difficult to interpret, suggest that in hypertensive patients an increased sympathetic drive in basal conditions might be associated with a reduced responsiveness of neural regulatory mechanisms as assessed by spectral analysis.

In an invasive study²⁵ in normotensive and hypertensive subjects undergoing 24-hour continuous recording of electrocardiogram and arterial pressure measured with a high-fidelity technique, the overall gain of the baroreceptive mechanisms was evaluated with the index (α) (see "Methodology"). This index underwent a clear circadian variation, being smaller during the day, and was found to be decreased at rest in the hypertensive group, confirming that neural buffering mechanisms appear attenuated in essential hypertension.⁷⁵

Ischemic Heart Disease

Experimental coronary artery occlusion can elicit neural and hemodynamic reflex responses that simultaneously include, from the heart, excitatory mechanisms mediated by cardiac sympathetic afferents^{11,76,77} and inhibitory mechanisms mediated by cardiac vagal afferents.^{12,77} In the clinical setting⁷⁸ of hyperacute phases of myocardial infarction, almost constant findings during the first 30 minutes after the onset of symptoms were signs of either sympathetic

hyperactivity, which were more frequent in the course of anterior localization, or vagal hyperactivity, which were more frequent during inferior wall infarction. Such an "autonomic disturbance," assessed on the basis of heart rate and arterial pressure values, coincided with the highest incidence of life-threatening arrhythmias. In an ongoing study (Figure 7), we are finding that at about 1–3 hours after the onset of symptoms, spectral analysis of RR variability reveals a sympathetic predominance that is particularly evident in anterior wall localization.

In relation to survival after myocardial infarction, a quite simple analysis in the time domain of heart rate variability, such as that offered by the use of either standard deviation or variance, has recently provided important clinical information.^{47,79–81} In particular, when applied on a large scale, a reduced standard deviation was found to carry a relevant prognostic value, being an independent predictor of mortality.⁴⁷ This reduction in standard deviation was attributed to a decreased vagal tone, which might also be reflected by a diminished total power of 24-hour spectral analysis,⁸² leading to the hypothesis^{47,80} of a simultaneous sympathetic predominance.

This hypothesis was fully supported by a study⁴⁸ in which we applied spectral techniques to analyze heart rate variability in a population of patients 2 weeks and 6 and 12 months after acute myocardial infarction. After 2 weeks, the LF component was significantly greater (69 ± 2 versus 53 ± 3 NU) and the HF component was significantly smaller (17 ± 1 versus 35 ± 3 NU) than in control subjects. This difference probably reflected an alteration of sympathovagal balance with a predominance of sympathetic activity. At 6 and 12 months, a progressive decrease in LF (62 ± 2 and 54 ± 3 NU) and increase in HF (23 ± 2 and 30 ± 2 NU) spectral components were observed, which suggested a normalization of sympathovagal interaction. Regarding the effects of tilt, 2 weeks

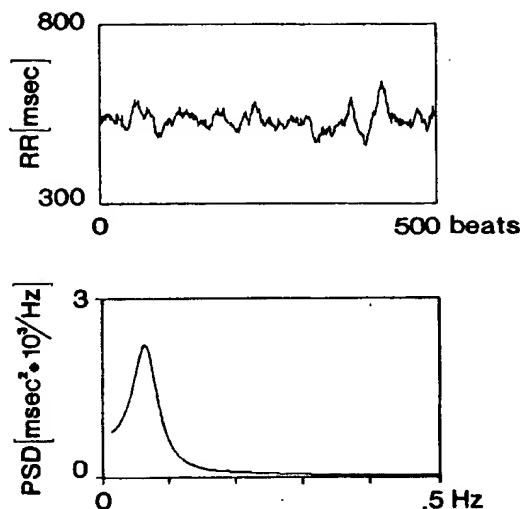


FIGURE 7. Spectral analysis of RR variability in a patient (62-year-old man) with an acute anterior myocardial infarction, recorded within 1 hour from onset of symptoms. Note predominant low-frequency component, suggesting sympathetic overactivity. PSD, power spectral density.

after myocardial infarction, this maneuver did not further modify the LF component of RR variability, whereas 1 year later, tilt was accompanied by an increase in the LF component of a magnitude similar to that observed in control subjects. One month after myocardial infarction, mental stress also failed to induce a significant increase in the already augmented LF component of RR variability.⁵⁸ More recently, the sympathetic predominance observed 2 weeks after myocardial infarction was studied during a 24-hour period and found to also persist at night, indicating that the normal circadian rhythm was markedly blunted.⁸³ The state of the sympathovagal balance in the period after the acute myocardial infarction has also been explored with the phenylephrine method,⁸⁴ and the results were compatible with the hypothesis of increased sympathetic and reduced vagal activities. All of these findings might provide a pathophysiological basis for the beneficial effects of β -adrenergic receptor blockade after myocardial infarction.

Regarding episodes of transient myocardial ischemia, as defined by electrocardiographic changes, in the limited number of patients reported by Bernardi et al⁸⁵ and in our investigation,⁴⁵ an increase in the LF component of RR variability was observed simultaneous with an increase in heart rate and independent of the occurrence of pain,⁸⁶ suggesting an excitatory reflex originating from the heart.^{11,76,77}

Finally, a significant relation has recently been found between the extent of coronary artery disease and the amplitude of HF component in RR variability,⁶² leading to the conclusion that a reduced cardiac

vagal function might correlate with angiographic severity of coronary impairment.

Cardiac Transplantation

The condition after human heart transplantation represents a clinical model of denervated heart that has prompted various studies with spectral analysis.⁸⁷⁻⁸⁹ In general, reduced total RR variance was found. However, although in some studies^{87,89} no discrete HF or LF components were consistently found in RR variability, Bernardi et al⁸⁸ described a small HF component interpreted to be independent of neural mechanisms. Furthermore, in one patient studied by Fallen et al⁸⁷ 33 months after transplantation, both LF and HF components were present, the latter increased by synchronous respiration and abolished by atropine. They concluded that spectral analysis could offer a unique method for establishing the state of possible reinnervation of human transplanted heart. Finally, Sands et al⁸⁹ reported an increased variance in patients developing an allograft rejection, a finding, however, that has been challenged by others.^{87,90}

Congestive Heart Failure

Congestive heart failure often appears to be accompanied by an increase in sympathetic activity.⁹¹ Reduced RR variability has been observed in patients with chronic congestive heart failure^{92,93} and interpreted as a sign of decreased parasympathetic activity. However, irrespective of its etiology, congestive heart failure can be characterized by various clinical manifestations, among which acute pulmonary congestion is likely to play a crucial role in determining the state of sympathovagal balance through a reflex enhancement of sympathetic activity.⁹⁴ In an ongoing study in patients with chronic congestive heart failure, we are finding that those in New York Heart Association functional class II or III are characterized by reduced variance and enhanced LF and reduced HF components, whereas a drastically diminished variance with only a residual HF component appears to be present in class IV patients. These preliminary observations suggest that signs of persistent sympathetic activation might be easier to recognize during the less advanced stages of the disease. On the other hand, in patients with severe chronic heart failure, Saul et al⁹² observed only very low frequency spectral components, usually centered near 0.015 Hz, which they attributed to a preserved sympathetic modulation; this conclusion might deserve further appraisal because this part of the spectrum is markedly affected by slow trends and DC component.

However, despite these uncertainties, spectral analysis appears adequate to assess the changes of the sympathovagal balance throughout the various stages and types of this complex clinical condition, thus contributing to the information required by a rational therapy.

Chagas' Disease

Both reduced parasympathetic⁹⁵ control of heart rate and impaired sympathetic⁹⁶ responsiveness have been reported in chronic Chagas' disease. In patients with positive serology and electrocardiographic alterations usually found in this disease but without heart failure, RR variance and power spectral profile at rest were not different from those of controls^{97,98}; however, when patients were standing, the usual increase in LF and decrease in HF were not present. This quantitative assessment of the altered neural modulation of heart rate might be useful in assessing the clinical progression of the disease.

Diabetic Neuropathy

Results of functional tests based on reflex cardiovascular responses have suggested a progressive deterioration of parasympathetic and, subsequently, sympathetic regulation in the course of diabetic visceral neuropathy.⁹⁹ Studies of RR variability indicated that diabetic patients have a reduced variance.^{31,46,49,100} Furthermore, in a group of patients without overt clinical signs of neuropathy, the spectral profile was normal at rest. However, during tilt⁴⁹ or standing,¹⁰¹ the increase in LF and decrease in HF components were markedly attenuated. This approach, which does not require that the patients engage in active tasks, like in the case of functional tests, could be even more appropriate for large-scale studies aimed at quantifying the early visceral neuropathy, its evolution, and possible therapies.

Future Lines of Research

Recent clinical investigation has clearly evidenced the more frequent occurrence of several types of acute cardiovascular events in the early morning hours,¹⁰² which is when sympathetic activity undergoes a sudden surge.²⁶ This suggests that neural mechanisms might play a crucial triggering role. Accordingly, a field of extreme relevance in which more information is needed on the neural mechanisms involved concerns acute cardiovascular events and, in particular, the prevention of sudden cardiac death.¹⁰³⁻¹⁰⁶ The inclusion of spectral analysis of cardiovascular variability in research protocols is now feasible and promising.

Summary

A consistent link appears to exist between predominance of vagal or sympathetic activity and predominance of HF or LF oscillations, respectively: RR variability contains both of these rhythms, and their relative powers appear to subserve a reciprocal relation like that commonly found in sympathovagal balance. In this respect, it is our opinion that rhythms and neural components always interact, just like flexor and extensor tones or excitatory and inhibitory cardiovascular reflexes, and that it is misleading to separately consider vagal and sympathetic modulations of heart rate. In humans and experimental

animals, functional states likely to be accompanied by an increased sympathetic activity are characterized by a shift of the LF-HF balance in favor of the LF component; the opposite occurs during presumed increases in vagal activity. In addition, LF oscillation evaluated from SAP variability appears to be a convenient marker of the sympathetic modulation of vasomotor activity.

Although based on indirect markers, the exploration in the frequency domain of cardiovascular neural regulation might disclose a unitary vision hard to reach through the assemblage of more specific but fragmented pieces of information.

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